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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/062,308	02/01/2002	David L. Rimm	YUA-001.01	2553
25181	7590	11/24/2006	EXAMINER	
			LIN, JERRY	
		ART UNIT		PAPER NUMBER
				1631

DATE MAILED: 11/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	10/062,308	RIMM ET AL.
	Examiner Jerry Lin	Art Unit 1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 31 August 2006.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 9, 10, 39 and 47-59 is/are pending in the application.
  - 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 9, 10, 39 and 47-59 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____ .
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____ .	6) <input type="checkbox"/> Other: _____ .

## DETAILED ACTION

1. Applicants' arguments and amendments, filed August 31, 2006, have been fully considered and they are deemed to be persuasive. Rejections not reiterated from previous office actions are hereby withdrawn. However, in light of the amendments, the following rejections and/or objections are newly applied as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

### *Claim Objections*

2. Claims 47, 57, and 59 are objected to because of the following informalities: the instant claims contain periods within the claim. Periods signify the end of a claim. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112, 2<sup>nd</sup> Paragraph*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 9, 10, 39, 47-50, 52-59, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. The term "high resolution" in claim 47 and 59 is a relative term which renders the claim indefinite. The term "high resolution" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary

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skill in the art would not be reasonably apprised of the scope of the invention. What is considered high resolution changes as the technology for imaging improves. What was once considered high resolution is no longer considered high resolution.

6. New claim 59 includes the limitation of "assess spillover." Although, the instant specification does mention "spillover" on page 12, line 17. The instant specification does not define "spillover." A search of art does not provide any well accepted definition of "spillover." It is unclear to what "spillover" is referring.

7. In addition, new claim 59 recites the limitation in c(2) "the other compartment." It is unclear to what compartment the instant claim is referring.

8. Claim 59 recites the limitation " first to second compartment intensity" in steps c(2). There is insufficient antecedent basis for this limitation in the claim. Previously the intensity referred to the stain, not the compartments.

### ***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 9, 10, 39, 47-53, 57 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Staines et al. (*The Journal of Histochemistry and Cytochemistry* (1988) Volume 36, number 2, pages 145-151) in view of Wood et al. (*Journal of Cell Biology* (1998) Volume 140, Number 3, pages 675-684).

The instant claims are drawn to a method for localizing and quantitating a particular biomarker by incubating a tissue sample with a first stain for a first subcellular compartment, a second stain for a second subcellular compartment, and a third stain for a biomarker; obtaining a high resolution image for each stain using an upright or inverted optical microscope; analyzing the first and second images and determining which pixels belong to which compartment; analyzing the third image and identifying the locations of the biomarker and quantitating the biomarker.

Regarding claim 47 and 59, Staines et al. teach a method that includes taking a tissue sample and incubating the sample with two stains for compartments and a biomarker (the Examiner interprets compartments to include anything from a organelle to a biomolecule or ion) (abstract; page 146), obtaining a high resolution image for each of the stains (page 147, left column), identifying the compartments by fluorescence intensity (page 147, right column; page 149, 150) (in addition it is noted that a weighted ratio of the first to second stain where one stain is not present indicates that the

assigned/identified compartment is accurate), identifying the location of the biomarker by fluorescence intensity (page 150).

However, Staines et al. does not teach using three stains or quantitating the biomarker based on intensity value.

Wood et al. teach quantitating the biomarker based on intensity value for an image of a stained tissue (abstract, page 677, right column bottom- page 678, right column top) and using an upright or inverted microscope (page 677).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the methods of Wood et al. and Staines et al. to gain the benefit of being able to determine the quantity of a biomarker through fluorescence intensity.

Staines et al. teaches that the goal of their method is to aid in the study of morphological bases of relationships and interactions between elements (abstract). A part of determining the relationships between elements in a tissue or cells is determining the quantity of the elements. Thus one of ordinary skill in the art would be motivated find means of determining the quantity of the elements. Wood et al. teach an automated method of analyzing the data in the images of tissue with fluorescent labels (abstract; page 677, right column bottom- page 678, right column top). Furthermore, Wood et al. teaches that the quantization of biomarkers at a location suggests the interaction between those biomarkers (page 684, left column bottom). Thus one of ordinary skill in the art at the time of the invention would be motivated to combine the methods of Staines et al. with Wood et al. given that both methods teach using fluorescent and both methods are concerned with determining the location of

biomarkers and determining the quantity of biomarkers to determine if there is an interaction between elements.

Regarding claim 9, Staines et al. show where the subcellular compartment is a nucleus (page 150).

Regarding claim 10, Staines et al. disclose where the biomarker is a peptides (abstract).

Regarding claim 39, Staines et al. disclose wherein the stain comprises a fluorophore (abstract).

Regarding claim 48, Wood et al. teach wherein the biomarker quantitation is determined by summing the intensity values within a compartment and dividing the sum by the number of pixels (abstract, page 677, right column bottom- page 678, right column top).

Regarding claim 49, Wood et al. teach regions not assigned to two compartments are assigned to a third compartment (page 677, Figure 2).

Regarding claim 50, Staines et al. teach wherein the tissue is about 5 microns (page 146, left column, top).

Regarding claim 67, Wood et al. disclose creating images with a CCD camera, which typically have resolutions of 1024x1024.

Regarding claim 52, Staines et al. disclose where one compartment is a nucleus (page 150) and Wood et al. disclose where one compartment is a cellular membrane (page 150).

Regarding claim 53, Staines et al. disclose wherein the tissue sample is fixed (page 146, left column, top).

Regarding claim 57, Wood et al. teach a method of subtracting the background (out of focus elements) from the images before determining the quantitation of the biomarker (page 677, right column bottom – page 678, left column top).

12. Claims 9, 10, 39, 47-57, 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Staines et al. (*The Journal of Histochemistry and Cytochemistry* (1988) Volume 36, number 2, pages 145-151) in view of Wood et al. (*Journal of Cell Biology* (1998) Volume 140, Number 3, pages 675-684) further in view of Forus et al. (*Journal of Clinical Pathology* (1999) Volume 52, pages 68-74).

The instant claims are drawn to a method for localizing and quantitating a particular biomarker by incubating a tissue sample with a first stain for a first subcellular compartment, a second stain for a second subcellular compartment, and a third stain for a biomarker; obtaining a high resolution image for each stain using an upright or inverted optical microscope; analyzing the first and second images and determining which pixels belong to which compartment; analyzing the third image and identifying the locations of the biomarker and quantitating the biomarker. In particular the claims are drawn to using a stain that reacts with cytokeratin, beta cantenin, alpha catenin, and vimentin; a fluorophore such as DAPI, Cy3 or Cy-5-tyramide; and a biomarker such as Her-2/neu, estrogen receptor, progesterone receptor, and epidermal growth factor receptor.

Staines et al. and Wood et al. are applied as above.

Regarding claims 10 and 54-56, neither Staines et al. or Wood et al. teach using a stain that reacts with cytokeratin, beta cantenin, alpha catenin, and vimentin; a fluorophore such as DAPI, Cy3 or Cy-5-tyramide; and a biomarker such as Her-2/neu, estrogen receptor, progesterone receptor, and epidermal growth factor receptor.

Regarding claims 54-56, Forus et al. teaches using a stain that reacts with cytokeratin (page 73, left column); a fluorophore such as DAPI (page 70, left column); and a biomarker such as Her-2/neu (page 70, left column).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the methods of Staines et al., Wood et al., and Forus et al. to gain the benefit of staining different compartments to study different biomarkers. Although Staines et al. and Wood et al. study specific biomarkers in tissue, their methods are not limited to these specific biomarkers. Rather their methods are applicable to study a variety of biological processes provide they have the right probes. Forus et al. provides additional new probes for one of ordinary skill in the art to utilized in the methods of Kononen et al. and Wood et al. Thus one of ordinary skill in the art would be motivated to combine the methods of Staines et al., Wood et al., and Forus et al. to study different biological processes involving cytokeratin or Her-2/neu.

13. Claims 9, 10, 39, 47-53, 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Staines et al. (*The Journal of Histochemistry and Cytochemistry* (1988) Volume 36, number 2, pages 145-151) in view of Wood et al. (*Journal of Cell*

Biology (1998) Volume 140, Number 3, pages 675-684) further in view of by Harris et al. (US 2003/0036855).

The instant claims are drawn to a method for localizing and quantitating a particular biomarker by incubating a tissue sample with a first stain for a first subcellular compartment, a second stain for a second subcellular compartment, and a third stain for a biomarker; obtaining a high resolution image for each stain using an upright or inverted optical microscope; analyzing the first and second images and determining which pixels belong to which compartment; analyzing the third image and identifying the locations of the biomarker and quantitating the biomarker. In particular the claims are drawn to applying a mask.

Staines et al. and Wood et al. are applied as above.

Regarding claims 58, neither Staines et al. or Wood et al. teach applying a mask.

Regarding claim 58, Harris et al. teach that the pixel locations in the plurality of pixels in the image of the first stain distribution are the pixel locations in the mask (page 11, paragraph 0143).

It would have been obvious to one of ordinary skill in the art to combine the method of Staines et al., Wood et al., and Harris et al. to gain the benefit of being able to determine the luminosity and density of the objects in the image. Harris et al. teach that using masks are beneficial because they provide more information about the image. Staines et al. aims to analyze the relationship of elements in a tissue. Thus one of ordinary skill in the art would be motivated to maximize the amount of information from a tissue sample. Harris et al. provides such a means through their masking technique.

One of ordinary skill in the art would be motivated to combine the methods of Staines et al. with Wood et al. and Harris et al. to gain more information for the images obtained from tissue samples.

### **Conclusion**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

***Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jerry Lin whose telephone number is (571) 272-2561. The examiner can normally be reached on 10:00am-6:30pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Representatives are available to answer your questions daily from 6 am to midnight (EST). When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It

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MICHAEL BORIN, PH.D  
PRIMARY EXAMINER

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